REMARKS

Claims 1-15 were pending. Claims 2, 4, 5 and 8-11 have been canceled without prejudice to their being pursued in any future application. Claims 14 and 15 were withdrawn by the Examiner. Claims 1, 14 and 15 have been amended. Therefore claims 1, 3, 6, 7 and 12-15 are currently pending.

Claim 1 has been amended to recite that the particles are "insoluble due to hydrophobic substituents bound to surface of the chelating cage," that "single units of paramagnetic chelate are released" and that the insoluble particles are degraded by "specific enzymes".

Claims 14 and 15 have been amended to depend from claim 1 and thus now recite all of the limitations of claim 1 and are now subject to rejoinder. Applicants therefore respectfully request that these claims be rejoined in the event claim 1 is found allowable.

Support for the above amendments can be found, for example, on page 5, lines 10-11, on page 6, lines 11-12 and in Fig. 7 of the published application. Thus, no new matter has been added by the foregoing amendments.

35 U.S.C. § 103(a)

Claims 1, 4-7 and 12 have been rejected under 35 U.S.C. § 103(a) as unpatentable over U.S. Pat. No. 4,985,233 ("Klaveness") as evidenced by the Encyclopedia Britannica Article "Reticuloendothelial System" ("Britannica") in view of U.S. Pat. No. 5,155,215 ("Ranney") because, *inter alia*, the cited combination allegedly describes water-soluble fragments which can be taken up by the reticuloendothelial system, internalized by cells and used in MRI imaging.

Claims 1, 4, 6 and 8-10 have been rejected under 35 U.S.C. § 103(a) as unpatentable over *Eur. J. Pharmaceutics and Biopharmaceutics, 2002, 53, p. 57-63* ("Shikata") in view of Ranney because, *inter alia*, when combined they disclose the accumulation of Gd-DTPA in chitosan nanoparticles which could be used in MRI.

Claims 1-3 and 6 are rejected under 35 U.S.C. . § 102(a) as being anticipated by Kabalka et al. *Mag. Res. In Medicine, 1988, 8, 53, p. 89-95*, as evidenced by Encyclopedia Britannica Article "Reticuloendothelial System" ("Britannica") in view of Ranney (applicants presume from the text of the rejection that this is a 103 rejection) because Kabalka and Ranney, *inter alia*, teaches Gd-DTPA containing liposomes which could be used for MRI.

Claims 1, 2 and 4-13 have been rejected under 35 U.S.C. § 103(a) as unpatentable over Klaveness et al. in view of U.S. Patent No. 5,498,421 ("Grinstaff") further in view of Ranney because the cited combination, *inter alia*, teaches in vivo delivery of a water-insoluble macromolecular particles associated with a polymeric shell which could be used for MRI.

In order for a claim to be found prima facie obvious, a prior art reference, or combination of references, must teach or suggest all limitations of the claim. MPEP § 2143. Furthermore, obviousness may not be found where the claimed invention is not predictable from the prior art. *KSR International Co. v. Teleflex Inc.*, 82 USPQ2d 1385 (2007); MPEP § 2143. Lastly, the prior art must be considered in its entirety, including art which teaches away from the claims. MPEP § 2141.02

Applicants address the above rejections in the order presented:

I. Klaveness, Britannica & Ranney

First, because the combination of Klaveness, Britannica and Ranney fails to teach or suggest each of the claim limitations (as amended), applicants respectfully traverse the § 103 rejection of claims 1, 4-7 and 12 over the aforementioned.[1]

Nowhere does Klaveness, alone or in combination with Britannica and Ranney teach or suggest a cellular imaging method where administered insoluble particles are degraded by enzymes specific to the cell type whose detection is sought. Likewise, Klaveness fails to teach or suggest the visualization of specific cells types or groups of cells, providing, for example, information concerning the nature of the cells (*e.g.* tumor cells) or proliferative processes starting from mother cells. (See Specification at p. 2, line 15 and p. 6 line 14). Put another way, Klaveness cannot provide the visualization of specific cell types because its particles are degraded across the organ as a whole as opposed to degradation by cell-type specific enzymes. Thus, the cited combination fails to provide a method of detecting if an enzyme is present and in what amount, whether transfection in gene therapy has been successful, whether a particular enzyme is over expressed or the detection of over-expressed tumor cell receptors.

Furthermore, Klaveness, alone or in combination with Britannica and Ranney, fails to teach or suggest a method of cellular labeling comprising the use of

[1] As an aside, the Examiner states that "MRI is at least a method of labeling cells which are imaged." Applicants respectfully disagree, instead MRI is a diagnostic technique which provides images of organs and tissues, as is confirmed by Ranney itself which states that "NMR intensity and relaxation images have been shown in recent years to provide another method of imaging internal structures and organs of living animals." (col. 1 lns 30-35).

particles that are insoluble due to hydrophobic substituents bound to the surface of the chelating cage. Instead Klaveness describes diagnostic agents which are water-insoluble, water swellable, hydroxyl group-containing particulate macromolecular compounds. This macromolecular material is described by Klaveness as including "polymeric and polymerized carbohydrates or a polymerized sugar alcohol or a derivative thereof." (See Klaveness col. 2 lines 10-25; col. 3 lines 1-5). Thus, the cited combination fails to teach or suggest particles that are insoluble due to hydrophobic substituents bound to the surface of the chelating cage.

Moreover, Klaveness, alone or in combination with Britannica and Ranney, fails to teach or suggest a method of cellular labeling in which insoluble particles are degraded by enzymes specific to the labeled cell types to form single units of paramagnetic chelates useful for MRI. Applicants note that the Examiner rejected applicants' argument that Klaveness does not teach a necessary step to MRI probes which the Examiner now contends is supplied by Britannica. (See 11/18/08 Office Action pp. 6 and 7). As a point of clarification, applicants did mean to deny that Klaveness's particles a degraded to smaller particles, but instead meant that Klaveness's particles are not degraded by specific cellular enzymes of the cells for which labeling is sought, so as to release single units of paramagnetic chelate suitable for MRI of the concerned cells by T_1 weighted sequences. Nevertheless, the particle degradation by Klaveness merely forms water-soluble fragments, not single units of paramagnetic chelates. Further, Britannica is silent on the degradation of particles by cell-type specific enzymes, teaching instead that the RES destroys engulfed material for excretion. Under Britannica's teaching, the particles would be <u>destroyed</u>, not degraded to single units of paramagnetic chelate useful

in MRI. Therefore, the cited combination fails to teach or suggest cellular labeling in which insoluble particles are degraded by enzymes specific to the labeled cell types to form single units of paramagnetic chelates useful for MRI.

Also, Klaveness merely describes the imaging of whole organs, not particular cells possessing the specific enzymes necessary to degrade the insoluble particles. In Klaveness, the degradable particles allow "investigation of the liver" where "insoluble particles which are not degradable in the body may be chosen for investigation of body cavities (e.g. the gastro intestinal tract, the bladder and the uterus)" (col. 5, lns 10-15, 40-50). The fact that organs are imaged in Klaveness does not mean that individual cell types are imaged.

Even when combined with Britannica and/or Ranney, the deficiencies of Klaveness are not cured. Britannica fails to cure Klaveness's deficiencies because, as pointed out above, it is silent on the degradation of particles by cell-type specific enzymes, teaching instead that the RES destroys engulfed material for excretion. And Ranney fails to cure the deficiencies of Klaveness because Ranney merely teaches that T_1 weighted enhancement may be obtained with the paramagnetic metal ion Galinium by selection of appropriate dose and pulse sequence. Ranney does not teach or suggest cellular labeling. Furthermore, applicants respectfully point out that an insoluble particle (even those containing paramagnetic chelates) would be relaxometrically silent (i.e. non-functional) when used in T_1 weighted sequences. (Specification p. 5 lines 9 and 10, Fig. 7). Thus, Ranney fails to teach or suggest the degradation of relaxometrically silent insoluble particles to form single units of paramagnetic chelates which can be used in MRI.

Therefore, for the above reasons, applicants respectfully request withdrawal of the § 103 rejection over Klaveness, Britannica and Ranney.

II. Shikata & Ranney

Second, because the combination of Shikata and Ranney fails to teach or suggest each of the claim limitations (as amended), applicants respectfully traverse the § 103 rejection of claims 1, 4, 6 and 8-10 over the aforementioned.

Shikata, alone or in combination with Ranney, fails to teach or suggest a method of cellular labeling comprising the use of particles that are insoluble due to hydrophobic substituents bound to the surface of the chelating cage. Instead Shikata merely describes the accumulation of Gd-DTPA in chitosan nanoparticles. Chitosan is (poly[B-(1-4)-2-amino-2-deoxy-D-glucopyranose) – a hydrophilic biocompatible and biodegradable polysaccharide derivative which lacks a hydrophilic substituent. (See Shikata at p. 57). Thus, Shikata's particles cannot have the same structure as particles that are insoluble due to hydrophobic substituents.

Furthermore, Shikata does not teach or suggest that chitosan nanoparticles are internalized in particular cells, degraded by cell-specific enzymes or release single units of paramagnetic chelate upon degradation.

Ranney fails to cure the deficiency of Shikata (*i.e.* does not provide a hydrophobic substituent) for the same reasons as discussed above.

For the above reasons, applicants respectfully request withdrawal of the § 103 rejection over Shikata and Ranney.

III. Kabalka, Britannica & Ranney

Third, because the combination of Kabalka, Britannica and Ranney fails to teach or suggest each of the claim limitations (as amended) and because Kabalka teaches away, applicants respectfully traverse the rejection of claims 1-3 and 6.

Like Klaveness, Kabalka, alone or in combination with Britannica and Ranney fails to teach or suggest a method of cellular labeling where administered insoluble particles are degraded by enzymes specific to the cell type whose detection is sought. Instead, Kabalka merely describes concentration of liposomes in macrophage rich organs. (Kabalka at p. 94). Any degradation of the Kabalka liposomes is due to "the more labile nature of the ester linkages in the acidic environment of the liver" – not to degradation by specific enzymes by which the insoluble particle is designed to be degraded (*e.g.* enzymes in a particular cell type such as tumor cells). Again, applicants point out that the liposomes of Kabalka only enable the imaging of an organ, not of a cell type possessing specific degradatory enzymes. In fact, in Kabalka, the local macrophages in the organ engulf the liposomes, thus allowing imaging of the organ. (Kabalka at p. 6 "a liver contrast of 5% was attained when 150 ul of the DTPA-SA labeled liposomes was injected"). Thus at best, Kabalka describes a method of targeting a macrophage-rich organ for imaging, not specific cell-types (*e.g.* tumor, transfected).

Even further, Kabalka fails to teach or suggest degradation into single units of paramagnetic chelate useful for MRI. *Applicants note that Kabalka does not mention 50% degradation, but 50% clearance, that is, the rate a substance is removed from an organ – in particular the kidneys – not enzymatic decomposition or transformation (i.e. degradation).* (Kabalka at p. 94). Instead Kabalka actually teaches away from

degradation as a means of imaging – Kabalka specifically touts the long half-life of its liposomes in the liver – with liposomes remaining intact in the liver 2 days from administration. (Kabalka at p. 94).

Lastly, Britannica and Ranney fail to cure the deficiencies of Kabalka for the reasons mentioned above.

Therefore, for the reasons discussed above, applicants respectfully request withdrawal of the § 103 rejection over Kabalka, Britannica and Ranney.

IV. Klaveness, Grinstaff & Ranney

Fourth, because the combination of Klaveness, Grinstaff and Ranney fails to teach or suggest each of the claim limitations (as amended), applicants respectfully traverse the rejection of claims 1, 2 and 4-13.

As explained above, Klaveness lacks particles which are insoluble due to hydrophobic substituents and does not mention a method of cellular labeling or a method of cellular labeling comprising enzymatic degradation by enzymes specific to the targeted cells.

Neither Grinstaff nor Ranney cure the deficiencies of Klaveness. Grinstaff fails to cure the deficiencies of Klaveness because it merely describes injectable suspensions which, by virtue of their being injected, can be manually targeted to particular organs. (Grinstaff col. 6 lines 44-47). Moreover, Grinstaff does not mention degradation of the particles to form single units of paramagnetic chelate for MRI imaging with T_1-weighted sequences. In sum, Grinstaff fails to mention a method of cellular labeling where particles are insoluble and relaxometrically silent in T_1-weighted MRI until they are taken up cells, and then degraded by those cells which possess the enzyme

necessary to degrade the particle. Lastly, Ranney fails to cure Klaveness's deficiencies for the reasons discussed prior.

Therefore, for the reasons discussed above, applicants respectfully request withdrawal of the § 103 rejection over Klaveness, Grinstaff and Ranney.

Conclusion

For the above discussed reasons, applicants respectfully submit that the presently pending claims, (claims 1 (as amended), 3, 6, 7, 12 and 13), are in condition for allowance. A speedy notice of allowability is therefore requested.

However, should the Examiner still be of the opinion that the presently pending claims are not in condition for allowance, applicants respectfully request an interview prior to the issuance of the next Office Action.

No fee, except the fee for a one month extension of time, is believed to be due for the filing of this Amendment and Response to Final Office Action. However, the Director is hereby authorized to charge any required fees and credit any overpayments to Deposit Account No. 50-0540.

Respectfully submitted,

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By: /Henry J. Cittone/

Henry J. Cittone, Reg. No. 57,206
Donald L. Rhoads, Reg. No. 34,705
KRAMER LEVIN NAFTALIS & FRANKEL LLP
1177 Avenue of the Americas
New York, NY 10036
(212) 715-9100 (telephone)
(212) 715-8000 (facsimile)